Immunogenicity and Safety of an Investigational Fully Liquid Hexavalent Combination Vaccine Versus Licensed Combination Vaccines at 6, 10, and 14 Weeks of Age in Healthy South African Infants

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Background: Assessment of primary vaccination of a new fully liquid, hexavalent investigational DTaP-IPV-Hep B-PRP-T vaccine (Hexaxim) in South African infants.

Methods: Infants were randomized to the following at 6, 10, and 14 weeks of age (Expanded Program on Immunization schedule): DTaP-IPV-Hep B-PRP-T (Group 1; N = 286); DTwP-Hib, hepatitis B, and OPV vaccines (Group 2; N = 286); or DTaP-IPV-Hep B-PRP-T vaccine with hepatitis B vaccine at birth (Group 3; N = 143). Antibody titers were measured before vaccination (pertussis toxoid, filamentous hemagglutinin) and postprimary vaccination (all valences). Noninferiority analyses were performed for Group 1 versus Group 2 for seroprotection rates. Safety was evaluated from parental reports.

Results: Noninferiority (Group 1 minus Group 2) was demonstrated for anti-HBs, -PRP, -diphtheria, -tetanus, and -polio 1, 2, 3 (lower 95% confidence interval for the difference was −8.20 to 3.46). Anti-HBs antibody titers ≥10 mIU/mL and anti-PRP ≥0.15 μg/mL were ≥95.4% in each group. Seroprotection rates were also high for the other antigens. Seroconversion rates (4-fold increase from pre- to postvaccination) were 93.6%, 83.2%, and 95.1% in Groups 1, 2, and 3, respectively, for anti-pertussis toxoid and 93.1%, 57.7%, and 90.0% for anti-filamentous hemagglutinin. Anti-HBs GMTs were 330, 148, and 1913 mIU/mL for Groups 1, 2, and 3, respectively. Reactogenicity was similar in each group. Fever ≥39.0°C occurred in 1.7%, 0.4%, and 0.0% of infants in Groups 1, 2, and 3, respectively; no extensive limb swelling, hypotonic-hyporesponsive episodes, or vaccine-related serious adverse events were reported.

Conclusions: The new, fully liquid, investigational hexavalent vaccine in the Expanded Program on Immunization schedule, with/without hepatitis B at birth, is highly immunogenic and safe compared with control vaccines, warranting further development.

Key Words: EPI schedule, pediatric, hexavalent, vaccination

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The investigational hexavalent vaccine is the latest addition to a range of AcXim family pediatric combination vaccines that are based on well-established diphtheria toxoid (D), tetanus toxoid (T), acellular (2-component) pertussis (aP), inactivated poliovirus (IPV), and *Haemophilus influenzae* type b polysaccharide conjugated to tetanus protein (PRP-T) antigens. The IPV and PRP-T components are WHO prequalified[1] (Imovax Polio and ActHib, respectively), and the AcXim family vaccines Tetraxim and Pentaxim have been licensed in more than 100 countries since 1997.[2] Currently, most hepatitis B antigens are based on recombinant yeast (eg, *Saccharomyces cerevisiae*) or recombinant mammalian cells (eg, Chinese Hamster Ovary). The new, fully liquid hexavalent vaccine incorporates a new, *Hansenula polymorpha*-derived, thiomersal-free hepatitis B (Hep B) component[3,4] with the established D, T, aP, IPV, and PRP-T antigens to create a hexavalent vaccine, DTaP-IPV-Hep B-PRP-T. Herein lies an important difference between this new, investigational hexavalent vaccine and a previous hexavalent vaccine that was suspended in 2005 because of poor long-term persistence of the response to the hepatitis B valence, namely the incorporation of a novel Hep B valence.

Pediatric combination vaccines are used routinely and have had enormous impact on childhood disease incidence.[5,6] Such vaccines have become the standard of care in many countries, although regional disparities remain with regard to specific components, for example, the use of aP versus whole-cell pertussis (wP) vaccines, or IPV versus the oral poliovirus vaccine (OPV). The inclusion of IPV in pediatric combination vaccines is important for both the pre- and post-polio eradication eras, consistent with the goal of the WHO's Global Polio Eradication Initiative.[7] In addition, reduced reactogenicity of aP compared with wP vaccines have been well-documented.[8] The investigational vaccine is being developed to provide a safer, better tolerated alternative to wP combination vaccines, and its use is expected to improve coverage and thus control of the targeted pediatric diseases.

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Sanofi Pasteur developed the protocol in conjunction with the study Investigators—Dr. Madhi, Dr. Mitha, Dr. Cutland, and Dr. Groome. Dr Eduardo Santos-Lima is employed by Sanofi Pasteur as Director, Clinical Development and Clinical Trial Leader for the investigational vaccine. The data were analyzed by Sanofi Pasteur in conjunction with the trial Investigators. As the Sponsor, Sanofi Pasteur paid for the conduct of the trial, but the Investigators received no direct payment from Sanofi Pasteur for conducting this study and have no financial ties to Sanofi Pasteur. The production of this publication was managed by Dr. Andrew Lane, who wrote the first draft and who is an employee of Sanofi Pasteur, with the full involvement of the Investigators and the Clinical Trial Leader. The manuscript was produced according to the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship, the European Medical Writers Association guidelines and Good Publication Practice. Each Investigator has therefore been involved in the review of draft manuscripts and has approved the final manuscript. The study Investigators received honoraria from Sanofi Pasteur for conference attendance for the presentation of the data reported in this manuscript, or for the presentation of other Sanofi Pasteur-sponsored clinical trials in which they were involved, or for the attendance of specific seminars at such conferences.

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Additional advantages of the investigational hexavalent vaccine are that it is fully liquid (eliminating the need for reconstitution prior to vaccination), and allows a reduced number of injections to improve compliance, facilitate administration, and reduce the error rate.

We compared the immunogenicity and safety of the investigational hexavalent vaccine to licensed comparators in the Expanded Program on Immunization (EPI) schedule of 6, 10, 14 weeks in South Africa. This follows previous evaluation of the Hep B candidate in South American adolescents and adults,[4] and assessments of the safety[9] and immunogenicity[10] of the hexavalent combination vaccine in Central and South American infants.

MATERIALS AND METHODS

Study Design/Participants

The protocol/informed consent form were approved by the independent ethics committees of 2 trial centers (the Chris Hani-Baragwanath Hospital and the Benmed Hospital, both in Johannesburg, Republic of South Africa [RSA]), and by the Medicines Control Council, RSA. The trial accorded to the Declaration of Helsinki (Edinburgh revision, October 2000) and International Conference on Harmonisation Good Clinical Practice (GCP), and applicable national and local regulations.

Each participant's parent(s) or legally acceptable representative gave written informed consent before the participant was included in the trial. If the parents were illiterate, an independent witness fully explained and signed the informed consent form. Only infants born to mothers documented as HIV negative after 24 weeks of gestation were included. If an HIV test result was not available, and for mothers with a negative HIV result but for whom a subsequent history was suggestive of acute seroconversion (SC) syndrome to HIV, a test was performed within 3 days of the infant's birth, prior to inclusion in the trial.

This Phase III, open-label, randomized, controlled 2-center trial included healthy infants at 0 to 3 days of age, born at full term of pregnancy (≥37 weeks) with birth weight ≥2.5 kg. Participants were excluded if febrile, if planning to take part in another clinical trial in parallel, if immunodeficient, if any blood-derived product had been administered since birth, or if any illness contraindicated trial inclusion. In addition, participants were not included if OPV had already been administered, if any vaccination other than BCG (or the trial vaccinations) was planned until 18 weeks of age, or if maternal HIV/HBsAg/hepatitis C seropositivity was known.

A 2-step randomization procedure created by Sanofi Pasteur's statistics department was used to assign participants to 1 of 3 groups; DTaP-IPV-Hep B-PRP-T at 6, 10, and 14 weeks of age without (Group 1) or with (Group 3) hepatitis B vaccination (Engerix B Pediatric) at birth (0–3 days of age), or DTwP//PRP-T (CombAct-Hib), recombinant hepatitis B (Engerix B Pediatric), and OPV with no hepatitis B vaccination at birth (Group 2). At the time of the trial initiation in RSA, DTwP//PRP-T, hepatitis B, and OPV vaccines were given at 6, 10, and 14 weeks of age according to the National Immunization Programme. At 0 to 3 days of age, participants were randomized to receive hepatitis B vaccination at birth (Group 3) or not (Groups 1 and 2). Those who did not receive hepatitis B vaccination at birth were further randomized at 6 weeks of age to receive the investigational (Group 1) or control (Group 2) vaccines.

Vaccines and Vaccine Administration

The vaccines' antigen composition is summarized in Table 1.

The investigational DTaP-IPV-Hep B-PRP-T vaccine (Hexaxim) was manufactured by Sanofi Pasteur, France, and supplied in a prefilled 0.5-mL syringe (S4106), which was shaken gently before injection. Commercial batches of CombAct-Hib (A2040–1 and B2048–2) were manufactured by Sanofi Pasteur, France; the vaccine was prepared at the time of injection by reconstituting freeze-dried PRP-T with DTwP suspension (0.5 mL).

The Engerix-B Pediatric vaccine was obtained commercially from GlaxoSmithKline as either vials (AHBVB208AM) or prefilled syringes (AHBVB223CE).

Commercial OPV (0.1 mL per dose) was manufactured by Sanofi Pasteur, France, (Z6507–2).

DTaP-IPV-Hep B-PRP-T and CombAct-Hib were administered into the anterolateral aspect of the right thigh; Engerix-B Pediatric was administered into the anterolateral aspect of the left thigh. Administration guidelines were provided for the vaccines.

Serology

A 3-mL blood sample was taken at 6 weeks of age (ie, prior to the first primary series vaccination) to determine anti-pertussis antibody levels (anti-PT and -filamentous hemagglutinin [FHA]) and a 5-mL sample was taken at 18 weeks of age (ie, 1 month after the third vaccination) to determine antibodies to all valences.

Serologic analyses were done at the Sanofi Pasteur Global Clinical Immunology Laboratory, USA. Anti-D and anti-poliovirus antibody titers were measured by seroneutralization; anti-T,

TABLE 1. Antigen Composition of Combination Vaccines

Antigen	DTaP-IPV-Hep B-PRP-T Vaccine (0.5 mL Dose)	Comparator Vaccines*		
		CombAct-Hib	Engerix B Pediatric	OPV
Purified D toxoid	≥20 IU	≥30 IU	—	—
Purified T toxoid	≥40 IU	≥60 IU	—	—
PT	25 μg	≥4 IU†	—	—
FHA	25 μg		—	—
Type 1 poliovirus, D antigen	40 units	—	—	$\geq 10^{(6.0)}$ $CCID_{50}$‡
Type 2 poliovirus, D antigen	8 units	—	—	$\geq 10^{(5.0)}$ $CCID_{50}$‡
Type 3 poliovirus, D antigen	32 units	—	—	$\geq 10^{(5.8)}$ $CCID_{50}$‡
Purified recombinant HBsAg	10 μg	—	10 μg	—
PRP-T	12 μg	10 μg	—	—

*For comparator vaccines, data are for CombAct-Hib (D, T, P antigens), Engerix B Pediatric (Hep B antigen), and OPV (polio 1, 2, 3 antigens); CombAct-Hib and Engerix B administered as 0.5 mL doses.

†Bordetella pertussis inactivated suspension, potency measured by the Kendrick test (mice intracerebral challenge assay).

‡$CCID_{50}$, 50% cell culture infective doses (viral infectious units).

OPV indicates oral poliovirus vaccine; D, diphtheria; T, tetanus; PT, pertussis toxoid; FHA, filamentous hemagglutinin; HBsAg, Sanofi Pasteur recombinant hepatitis B surface antigen; PRP-T, *Haemophilus influenzae* type b polysaccharide conjugated to tetanus protein.

anti-PT, and anti-FHA by enzyme-linked immunosorbent assay; anti-HBs using the commercially available VITROS anti-HBs assay; and anti-PRP by radioimmunoassay.

Reactogenicity and Safety

For routine evaluation of reactogenicity and safety, each participant was observed by the investigator for 30 minutes after each vaccination to monitor immediate adverse events. In addition, the parent(s) or legally responsible representative used diary cards for 7 days after vaccination to record the start, end, and intensity of predefined (solicited) injection site (pain, erythema, and swelling) and systemic (pyrexia, vomiting, crying, somnolence, anorexia, and irritability) reactions. All solicited events were considered to be related to the vaccination, and any event related to vaccination was termed a "reaction."

In addition, the parent(s)/legally responsible representative recorded the start/end and intensity of any nonsolicited events. All nonsolicited injection site events were considered to be related to the vaccination and so were recorded as injection site reactions; the relationship to the vaccination for nonsolicited systemic events was assessed by the Investigator. Each adverse event was categorized as Grade 1, 2, or 3 by the Investigator (Table 2 for definitions).

Serious adverse events (SAEs) were collected until 6 months after the last vaccination.

Statistical Analyses

The primary objective was to demonstrate that the DTaP-IPV-Hep B-PRP-T vaccine does not induce a lower immune response (in terms of seroprotection [SP]) as compared with the comparators, when no hepatitis B vaccination is given at birth (Group 1 vs. Group 2). Secondary objectives included the description immunogenicity in Group 3, and the description of reactogenicity and safety profiles in each group.

Defined correlates of SP[11,12] have been established for D, T, polio types 1, 2, 3, Hib, and Hep B (Table 3). A noninferiority test was done using the 95% 2-sided confidence interval (CI) of the difference between the SP rates, with noninferiority being concluded if the lower limit of the 2-sided 95% CI for the group difference was $>-10\%$ for D, T, Hep B, and PRP, and $>-5\%$ for the 3 polio antigens. The 95% CI was calculated on the basis of the

TABLE 2. Solicited Injection Site and Systemic Adverse Reactions Occurring Within 8 Days (Day 0–7) After Any Dose of Vaccine

	Group 1 (N = 243)	Group 2 (N = 242)		Group 3 (N = 137)
		CombAct Hib	Engerix B Pediatric	
Injection site reactions*				
Any	89.9 (85.3–93.4)	95.0 (91.4–97.4)		92.6 (86.9–96.4)
Grade 3	12.2 (8.4–17.1)	16.4 (11.9–21.7)		8.8 (4.6–14.9)
Pain				
Any	85.2 (80.1–89.5)	88.2 (83.4–92.0)	81.5 (76.0–86.2)	87.5 (80.7–92.5)
Grade 3	7.2 (4.2–11.2)	10.1 (6.6–14.6)	5.9 (3.3–9.7)	5.1 (2.1–10.3)
Erythema				
Any	67.8 (61.4–73.7)	72.7 (66.6–78.2)	55.9 (49.3–62.3)	67.4 (58.8–75.2)
Grade 3	3.8 (1.8–7.1)	6.3 (3.6–10.2)	2.9 (1.2–6.0)	1.5 (0.2–5.2)
Swelling				
Any	55.1 (48.5–61.5)	63.0 (56.6–69.2)	42.0 (35.7–48.6)	47.8 (39.2 56.5)
Grade 3	3.8 (1.8–7.1)	4.2 (2.0–7.6)	2.1 (0.7–4.8)	2.9 (0.8–7.4)
Systemic reactions				
Any	92.0 (87.8–95.1)	92.4 (88.3–95.5)		94.1 (88.7–97.4)
Grade 3	15.2 (10.9–20.4)	18.9 (14.1–24.5)		11.8 (6.9–18.4)
Pyrexia				
Any	44.5 (38.0–51.1)	33.2 (27.2–39.6)		33.1 (25.3–41.7)
Grade 3	1.7 (0.5–4.3)	0.4 (0.0–2.3)		0.0 (0.0–2.7)
Vomiting				
Any	44.9 (38.5–51.5)	42.0 (35.7–48.6)		40.0 (31.7–48.8)
Grade 3	5.9 (3.3–9.8)	2.9 (1.2–6.0)		4.4 (1.6–9.4)
Crying				
Any	76.3 (70.3–81.5)	78.2 (72.4–83.2)		83.0 (75.5–88.9)
Grade 3	6.4 (3.6–10.3)	8.4 (5.2–12.7)		6.7 (3.1–12.3)
Somnolence				
Any	60.6 (54.0–66.9)	60.1 (53.6–66.4)		57.8 (49.0–66.2)
Grade 3	3.8 (1.8–7.1)	3.8 (1.7–7.1)		5.9 (2.6–11.3)
Anorexia				
Any	46.6 (40.1–53.2)	55.9 (49.3–62.3)		49.3 (40.6–58.0)
Grade 3	3.8 (1.8–7.1)	5.5 (2.9–9.2)		3.7 (1.2–8.4)
Irritability				
Any	66.5 (60.1–72.5)	69.3 (63.0–75.1)		69.6 (61.1–77.2)
Grade 3	7.6 (4.6–11.8)	6.7 (3.9–10.7)		3.7 (1.2–8.4)

Data are % participants (95% CI).

'Any' = all cases, irrespective of grade.

*For injection site reactions, only CombAct-Hib data from Group 2 included in this comparison.

N is the number of subjects with available safety data post-injection Grade 1, 2, and 3 pain were defined as 'minor reaction when injection site is touched,' 'cries and protests when injection site is touched,' and 'cries when injected limb is moved or the movement of the injected limb is reduced.' For erythema and swelling, a diameter of <2.5 cm was Grade 1, from 2.5 to <5 cm was Grade 2 and ≥5 cm was Grade 3. Grade 1, 2, and 3 fever were defined as rectal temperature ≥37.4°C to 37.9°C, ≥38.0°C to 38.9°C, and ≥39.0°C, respectively. Other systemic symptoms were defined as: vomiting (Grade 1–Grade 2, 1–5 episodes/day; Grade 3, ≥6 episodes/day) abnormal crying (Grade 1–Grade 2, ≤3 hours; Grade 3, >3 hours), drowsiness, (Grade 1–Grade 2, unusually sleepy; Grade 3, sleepy most of the time) loss of appetite (Grade 1–Grade 2, missed 1–2 meals; Grade 3, missed ≥3 meals), and irritability (Grade 1–Grade 2, easily consolable or needs increased attention; Grade 3, inconsolable).

CI indicates confidence interval.

TABLE 3. Seroprotection/Seroconversion Rates 1 Month After the 3-Dose Primary Vaccination Series Including Statistical Analysis for the Primary Objective (PP Analysis Set)

Antibody	Threshold	Group 1 (N = 220)	Group 2 (N = 212)	Group 3 (N = 123)	Group 1 Minus Group 2
Anti-Hep B	≥10 mIU/mL*	95.7 (91.6 to 98.1)	95.4 (91.4 to 97.9)	99.0 (94.4 to 100.0)	0.29 (−4.26 to 4.77)
	≥100 mIU/mL	78.8 (72.2 to 84.5)	65.5 (58.3 to 72.1)	96.9 (91.3 to 99.4)	NC
Anti-PRP	≥0.15 μg/mL*	95.4 (91.8 to 97.8)	100.0 (98.3 to 100.0)	97.5 (93.0 to 99.5)	−4.57 (−8.20 to −1.84)
	≥1.0 μg/mL	79.5 (73.5 to 84.6)	92.5 (88.0 to 95.6)	79.5 (91.3 to 86.3)	NC
Anti-D	≥0.01 IU/mL*	97.6 (94.4 to 99.2)	96.1 (92.5 to 98.3)	95.1 (89.6 to 98.2)	1.46 (−2.20 to 5.31)
	≥0.1 IU/mL*	39.8 (33.1 to 46.8)	13.6 (9.2 to 19.0)	39.3 (30.6 to 48.6)	NC
Anti-T	≥0.01 IU/mL*	100.0 (98.3 to 100.0)	100.0 (98.3 to 100.0)	100.0 (97.0 to 100.0)	0.00 (−1.77 to 1.80)
	≥0.1 IU/mL*	100.0 (98.3 to 100.0)	100.0 (98.3 to 100.0)	100.0 (97.0 to 100.0)	NC
Anti-polio 1	≥8 1/dil*	100.0 (98.0 to 100.0)	93.0 (88.4 to 96.2)	99.0 (94.8 to 100.0)	6.95 (3.46 to 11.5)
Anti-polio 2	≥8 1/dil*	98.5 (95.6 to 99.7)	100.0 (98.1 to 100.0)	98.2 (93.8 to 99.8)	−1.53 (−4.40 to 0.675)
Anti-polio 3	≥8 1/dil*	100.0 (98.0 to 100.0)	98.3 (95.2 to 99.7)	100.0 (96.3 to 100.0)	1.68 (−0.668 to 4.81)
Anti-PT	4-fold increase†	93.6 (88.8 to 96.8)	83.2 (75.9 to 89.0)	95.1 (89.0 to 98.4)	NA
Anti-FHA	4-fold increase†	93.1 (88.0 to 96.5)	57.7 (48.7 to 66.3)	90.0 (81.9 to 95.3)	NA

Data are % participants (95% CI), calculated according to the subjects available for the endpoint.

*Primary endpoint (with statistical test for noninferiority between Groups 1 and 2).

†Compared to pre-first primary series dose data.

PP indicates per protocol; CI, confidence interval; Hep B, hepatitis B surface antigen; PRP, polyribosylribitol phosphate; D, diphtheria; T, tetanus; PT, pertussis toxin; FHA, filamentous hemagglutinin; NC, not calculated (secondary assessment criteria); NA, not applicable.

TABLE 4. Geometric Mean Titers 1 Month After the 3-Dose Primary Vaccination (PP Analysis Set)

Antibody	Group 1 (N = 220)	Group 2 (N = 212)	Group 3 (N = 123)
Anti-Hep B (mIU/mL)	330 (259–420)	148 (120–181)	1913 (1457–2513)
Anti-PRP (μg/mL)	3.31 (2.69–4.08)	5.18 (4.47–6.00)	3.83 (2.92–5.02)
Anti-D (IU/mL)	0.074 (0.062–0.088)	0.040 (0.035–0.046)	0.074 (0.059–0.094)
Anti-T (IU/mL)	1.51 (1.37–1.65)	1.88 (1.70–2.07)	1.33 (1.17–1.51)
Anti-polio 1 (1/dil)	579 (478–702)	198 (153–256)	557 (410–756)
Anti-polio 2 (1/dil)	620 (512–750)	446 (374–533)	371 (281–489)
Anti-polio 3 (1/dil)	975 (812–1170)	228 (185–280)	811 (645–1020)
Anti-PT (EU/mL)	332 (304–362)	191 (147–249)	288 (256–323)
Anti-FHA (EU/mL)	207 (190–226)	37.4 (33.4–41.9)	188 (166–212)

Data are GMT (95% CI), calculated according to the subjects available for the endpoint.

PP indicates per protocol; CI, confidence interval; Hep B, hepatitis B surface antigen; PRP, polyribosylribitol phosphate; D, diphtheria; T, tetanus; PT, pertussis toxin; FHA, filamentous hemagglutinin.

Wilson score method without continuity correction as described by Newcombe.[13]

As there are no universally accepted correlates of protection for pertussis antibodies, SC rate was predefined as a ≥4-fold increase from baseline in antibody titer (EU/mL). Thus, anti-PT and anti-FHA were the only antibodies measured before and after the primary vaccination series. Anti-PT and anti-FHA were not compared between Groups 1 and 3 (aP vaccine) and Group 2 (wP vaccine).

Secondary immunogenicity endpoints were the descriptive analyses of antibody titers and other predefined thresholds for all valences in each group (Tables 3, 4). In addition, safety was assessed by group.

It was planned to include a total of 715 participants, randomly allocated to Group 1, 2, or 3. Of these, 572 participants were to be included in Groups 1 and 2 to provide 458 evaluable participants for the noninferiority analysis (assuming an attrition rate of approximately 20%); this sample size was calculated using the Farrington and Manning formula[14] and based on a type 1 error of 2.5% (1-sided hypothesis) to obtain an overall power of 90%. The sample size for Group 3 (approximately 50% of Groups 1 and 2) was arbitrary (only used for descriptive analyses).

The intent-to-treat (ITT) analysis set comprised all participants who received ≥1 dose of vaccine, analyzed by randomization group. The per-protocol (PP) analysis set comprised ITT participants who received the 3 doses of primary series with no protocol deviations. The Safety Analysis Set comprised participants who received ≥1 dose of vaccine, analyzed by vaccine received. The primary hypothesis of noninferiority was tested on the PP analysis set and confirmed using the ITT analysis set. The Safety Analysis Set was used for the safety analysis.

All analyses (except for SAEs) were performed using SAS software, Version 9.1 (SAS Institute, Cary, NC).

RESULTS

Participants Studied

A total of 715 participants were present at 0 to 3 days of age for the first step of the randomization; 93 of these withdrew before receiving 1 of the 2 study combined vaccines at 6 weeks of age (86 in Groups 1 or 2 and 7 in Group 3). Participant disposition is summarized in Figure 1.

Of the 622 participants who present for the first primary series vaccination, 243 (no hepatitis B at birth) received DTaP-IPV-Hep B-PRP-T (Group 1), 242 (no hepatitis B at birth) received CombAct-Hib+Engerix B Pediatric+OPV (Group 2), and 137 who had received hepatitis B at birth received DTaP-IPV-Hep B-PRP-T (Group 3).

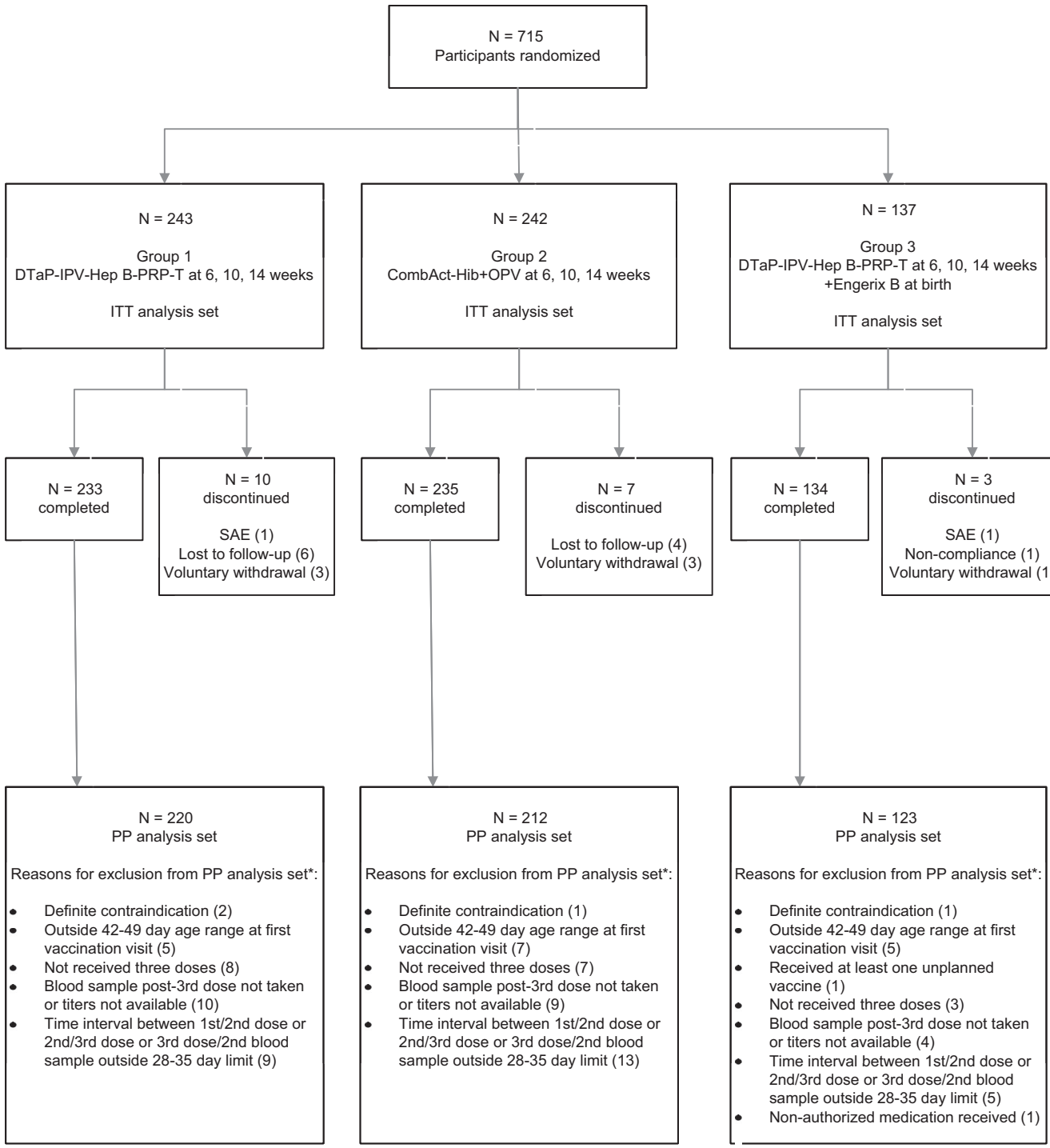

FIGURE 1. Participant disposition and analysis sets. *There may be more than 1 reason per participant. N indicates number; PP, per protocol; ITT, intent-to-treat.

Of the 622 participants who were present for the first primary series vaccination, 602 completed the primary series and 596 completed the 6-month follow-up for SAEs. The trial took place from August 2006 to November 2007.

Demographic characteristics were similar in each group. At 6 weeks of age (second randomization step), 46% to 51% of the participants were male and the median age was 43.0 to 44.0 days; the median birth weight was 3.10 to 3.20 kg.

Immunogenicity

Seroprotection for anti-Hep B, anti-PRP, anti-D, anti-T, and anti-polio 1, 2, and 3, was high for all groups at 1 month after the

primary series vaccination (Table 3). For each of these antigens, noninferiority of the investigational DTaP-IPV-Hep B-PRP-T combined vaccine versus the control vaccines was demonstrated on the basis of 95% CIs of the difference of Group 1 minus Group 2 (Table 3).

The percentage of participants with a Hep B titer ≥100 mIU/mL was higher for Group 1 (78.8%) as compared with Group 2 (65.5%). Anti-PRP ≥1.0 μg/mL for Group 2 (92.5%) was higher than Group 1 (79.5%); anti-D ≥0.1 IU/mL was higher for Group 1 (39.8%) than Group 2 (13.6%). Anti-FHA and anti-PT 4-fold increases were 93.6% and 93.1% (Group 1), and 83.2% and 57.7% (Group 2).

In Group 3 (hepatitis B at birth), the percentage of participants with a Hep B titer ≥100 mIU/mL (96.9%) was higher than for Groups 1 (78.8%) and 2 (65.5%), and was similar to the primary SP endpoint (≥10 mIU/mL) (99.0%). With the exception of Hep B, Groups 1 and 3 were comparable for all thresholds, and there was no difference based on PT and FHA SC rates.

The Hep B GMT (Table 4) response to the primary vaccination series was approximately 2-fold higher for Group 1 than Group 2. The Hep B GMT for Group 3 (hepatitis B at birth) was approximately 6-fold higher than for Group 1. For the remaining antigens, there were no GMT differences, except for anti-polio 2 (higher in Group 1 than Group 3), anti-PRP, and anti-T (higher for Group 2 than Group 1), and anti-D, anti-polio 1, and 2 (higher for Group 1 than Group 2).

Safety and Tolerability

Only a single immediate event was reported (Grade 1 upper respiratory tract infection after the third vaccination of DTaP-IPV-Hep B-PRP-T [Group 1]). This was not considered to be related to the vaccination and lasted 25 days.

Overall, the incidence of injection site and systemic reactions, and the incidence of Grade 3 reactions were similar for Groups 1 and 2 (Table 2). For individual reactions, pyrexia was slightly more frequent in Group 1 than Group 2 and anorexia more common in Group 2 than Group 1. The incidence of the each type of injection site reaction was consistently lower (for all reactions and for those rated Grade 3) for Group 1 compared with Group 2. For the individual systemic reactions, with the exception of pyrexia and anorexia the incidence was similar in Groups 1 and 2. The incidence of injection site or systemic reactions in Groups 1 and 3 was comparable.

For unsolicited events, the incidence was similar in each of the 3 groups, ranging from 23.5% to 26.6% of participants (7 days postvaccination) and 58.1% to 63.3% of participants (28 days postvaccination). The majority were medical conditions common in early childhood and few were considered to be related to the vaccination.

A total of 56 participants experienced 80 nonfatal SAEs, the incidence being similar in each group, and none considered to be related to the vaccination. Four subjects experienced fatal SAEs—again, none was considered to be related to the vaccination (death of natural causes during sleep before the first primary series vaccination; bronchitis approximately 1 month after the third vaccination in Group 1; pneumonia approximately 1 month after the second vaccination in Group 3; HIV positivity, respiratory tract infection and suspected tuberculosis aged approximately 10 months in Group 1).

DISCUSSION

Our primary objective was to evaluate the immunogenicity of a new investigational, fully liquid pediatric hexavalent vaccine, DTaP-IPV-Hep B-PRP-T, compared with licensed vaccines available at the time of trial initiation. These vaccines were administered in the challenging EPI schedule of 6, 10, 14 weeks of age without hepatitis B vaccination at birth according to the South African vaccination schedule.[15] A third group was included to assess the effect of a birth dose of hepatitis B on the immunogenicity and safety of DTaP-IPV-Hep B-PRP-T. This article reports on 1 study of many that are included in the clinical development of this new product in a range of ethnic populations and primary series administration schedules: the results of the other studies, using other primary series schedules, will be published in an ongoing manner. In our article, we only report on the 6-, 10-, 14-week schedule.

The immunogenicity of the Hep B, PRP, D, T, and the 3 polio antigens was compared between Groups 1 and 2. For the pertussis components, no intergroup comparisons were made as the investigational vaccine contained aP antigens whereas the comparator contained wP antigens. The primary statistical analysis demonstrated noninferiority of the investigational vaccine for each antigen tested, using predefined surrogates of seroprotection and predefined criteria for noninferiority. The D, T, aP, IPV, and PRP antigen responses reflect their strong immunogenicity observed in previous clinical trials of Pentaxim administered in the same 6-, 10-, 14-week schedule in the Philippines, India, and RSA.[16–18]

The response to the new Hep B antigen of the investigational vaccine administered in the EPI schedule with or without hepatitis B at birth is of particular interest. At the threshold of 10 mIU/mL, >95% were protected in each group, with no difference between groups and no effect of the additional hepatitis B dose at birth. This compares favorably to an SP rate of 77.7% for the hepatitis B component of a licensed aP-combined vaccine administered at 6, 10, 14 weeks in the absence of a birth dose of hepatitis B.[19] The licensed vaccine is not fully liquid, but has been available for several years and is used successfully and extensively globally.[20] Although the threshold of 10 mIU/mL is accepted as a correlate for hepatitis B seroprotection,[21] we also assessed the percentage of participants with a titer ≥100 mIU/mL. At this higher threshold, the response was higher in participants who received the investigational vaccine than the hepatitis B monovalent vaccine comparator. The addition of a birth dose of Hep B further augmented the response, as expected.[22] Using the accepted threshold of 10 mIU/mL, it appears that the addition of Hep B at birth does not significantly affect the Hep B response, and that even in the absence of Hep B at birth, vaccinees are protected.

For the other, secondary, thresholds used to assess the immune response, there were small group differences, but because the magnitude of the responses was quite high none are considered to be of clinical importance. Overall, the investigational vaccine was as immunogenic as the comparators.

There were no marked differences in overall safety profile between participants who received the investigational vaccine and those who received the comparator vaccines. Furthermore, the addition of the birth dose of hepatitis B had no adverse effect on the reactogenicity of the investigational vaccine, as expected.[22]

Acellular pertussis vaccines have been well documented to result in a lower incidence of fever (especially severe fever) than wP vaccines.[8] We observed that the incidence of fever was slightly higher in Group 1 (aP) compared with Group 2 (wP) but not when Group 3 (aP) was compared with Group 2 (wP). The reason for this is unclear. A previous study with the investigational vaccine reported less pyrexia compared with a wP vaccine.[9] Since the duration of fever was short and the number of children experiencing Grade 3 reactions was very low, the difference is not considered clinically significant. On the basis of these immunogenicity and safety data, the use of this new DTaP-IPV-Hep B-PRP-T AcXim family vaccine is warranted in countries using the chal-

lenging EPI primary series schedule, whether a dose of hepatitis B is given at birth or not. Antibody persistence data and booster response data will be reported in future publications.

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